

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



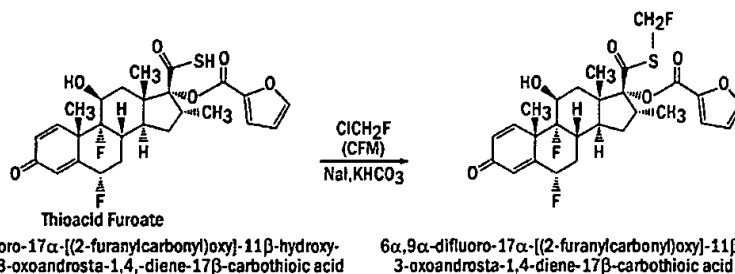
(43) International Publication Date  
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number  
**WO 03/013427 A2**

- (51) International Patent Classification<sup>7</sup>: **A61K**
- (21) International Application Number: **PCT/US02/24586**
- (22) International Filing Date: **1 August 2002 (01.08.2002)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:  
**60/367,341**      **3 August 2001 (03.08.2001)**      **US**
- (71) Applicant (for all designated States except US):  
**SMITHKLINE BEECHAM CORPORATION**  
[US/US]; One Franklin Plaza, Philadelphia, PA 19101 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **PARTRIDGE, John, Joseph** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **WALKER, Dwight, Sherod** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US).
- (74) Agents: **LEVY, David, J.** et al.; GlaxoSmithKline, Corporate Intellectual Property Department, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US).
- (81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.**
- (84) Designated States (regional): **ARIPO** patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), **Eurasian** patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), **European** patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), **OAPI** patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **A METHOD FOR PREPARING FLUTICASONE DERIVATIVES**



(57) Abstract: A method for preparing 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester from a thiocarboxylic acid by reacting the thiocarboxylic acid with a solution containing chlorofluoromethane and a mild base medium at a temperature in the range of -60° C to 90° C.

WO 03/013427 A2

6

## A METHOD FOR PREPARING FLUTICASONE DERIVATIVES

### 5 CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority benefit to U.S. Provisional Application No. 60/367341, filed 3 August 2001.

### 10 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to the preparation of fluticasone derivatives. More particularly, the invention relates to the preparation of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester.

### 15 BACKGROUND OF THE INVENTION

Glucocorticosteroids, such as fluticasone derivatives, are well-known anti-inflammatory and anti-allergic compounds of the androstane series. Glucocorticosteroids are known to have anti-inflammatory properties and are thus widely used for the treatment of inflammatory disorders or diseases such as asthma and rhinitis. Such compounds have potentially beneficial anti-inflammatory or anti-allergic effects, particularly upon topical administration, demonstrated by, for example, their ability to bind to the glucocorticoid receptor and to elicit a response via that receptor. These compounds are thus useful in the treatment of inflammatory and/or allergic disorders.

20 Examples of disease states in which fluticasone derivatives are effective include skin diseases such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis and certain hypersensitivity reactions. Inflammatory conditions of the nose, throat or lungs, such as asthma (including allergic-induced asthmatic reactions), rhinitis (including hay fever), nasal polyps, chronic obstructive pulmonary disease, interstitial lung disease, fibrosis, inflammatory bowel conditions such as ulcerative colitis and Crohn's Disease  
30 have all responded favorably to the administration of fluticasone derivatives as well as certain auto-immune diseases such as rheumatoid arthritis. The compounds can also be used in the treatment of conjunctivitis.

Fluticasone derivatives have proven to be useful in human or veterinary medicine, particularly as anti-inflammatory and anti-allergic agents. The compounds can be

incorporated in a suitable pharmaceutically accepted carrier and can be administered to a user topically as a ointment, lotion, cream, gel or foam or by transdermal patches, powders, sprays, aerosols, capsules or cartridges, the latter for use in an inhaler or insufflator or drops, (e.g. eye or nose drops), solutions/suspensions for nebulisation, suppositories, pessaries, retention enemas and chewable or suckable tablets or pellets.

Although the fluticasone derivatives of the present invention are obviously highly useful, preparation of fluticasone derivatives has been fraught with certain limitations and adverse environmental concerns. Specifically, fluticasone derivatives are typically prepared by reacting a halo-fluoromethane, such as bromofluoromethane (BFM), iodofluoromethane (IFM) or chlorofluoromethane (CFM), with one or more reagents. Representative processes are disclosed in Phillipps, et al., "Synthesis and Structure – Activity Relationships in a Series of Anti-Inflammatory Corticosteroid Analogues, Halomethyl Androstane – 17  $\beta$  – Carbothioates and – 17  $\beta$  Carboselenoates", *J. Med. Chem.*, vol. 37, pp. 3717-3729 (1994) (hereinafter "Phillipps, et al.") and Israel Pat. No. 109,656 (May 24, 1998).

In Phillipps, et al., a process for synthesizing fluticasone derivatives is disclosed wherein a fluoromethyl thioester is prepared from a potassium salt of carbothioic acid (also named thiocarboxylic acid or thioacid), using IFM or BFM. Israel Pat. No. 109,656, also discloses a process for synthesizing fluticasone propionate using BFM as a reagent, and also discloses the use of CFM for this purpose.

These prior art halo-fluoromethane utilizing processes possess certain disadvantages. A major drawback of the noted BFM processes is that BFM is a highly toxic, ozone depleting substance identified under the Montreal Protocol, an international agreement addressing the issue of green house gasses. IFM, on the other hand, suffers from the drawbacks of being generally unstable and is presently not commercially available.

CFM is described in Israel Pat. No. 109,656 as being useful in processes incorporating undesirable conditions and yielding undesirable results. The undesirable conditions, results and, hence, drawbacks of the prior art CFM processes include the following: (i) the useful reactions using CFM are run at very high temperatures (e.g., 100° C) and pressures (e.g., ~ 200 atm), which can be extremely hazardous, (ii) there is minimal conversion to desired product even with 9 molar equivalents of CFM, (iii) there is low

product yield, and (iv) there is significant impurity content in final products. Such conditions would be in keeping with a perception that CFM is relatively non-reactive and, hence, inappropriate for this use.

5 It is therefore an object of the present invention to provide a simple and comparatively environmentally "green" process for preparing fluticasone derivatives when compared to BFM.

It is a further or alternative object of the present invention to provide a method for synthesizing fluticasone derivatives without the need for using BFM.

10 It is a further or alternative object of the present invention to provide a method for synthesizing fluticasone derivatives from thiocarboxylic acids without the need for using IFM, or producing IFM as an intermediate compound.

It is a still further or alternative object of the present invention to provide a method for synthesizing fluticasone derivatives that produces high yields of products with minimal impurities.

15 A further or alternative object of the first aspect of the present invention is to provide a method of synthesis for fluticasone derivatives that may be operated under relatively non-hazardous conditions.

A further objective of one alternative aspect of this invention is to provide a pharmaceutical composition made from a process offering one or more of the above  
20 advantages.

A further or alternative objective of the invention is provide an improved method of producing fluticasone derivatives, and in particular the novel derivative, 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrost-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester. Improvements may include increased production  
25 rates, decreased costs, or use of fewer and/or safer reactants.

## **SUMMARY OF THE INVENTION**

In accordance with the above objects and those that will become apparent below, the present invention relates to a process for preparing 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester comprising reacting a thiocarboxylic acid with a solution  
5 containing chlorofluoromethane and a mild base medium preferably at a temperature in the range of -20° C to 50° C, more preferably, -15° C to 50° C. In a preferred embodiment of the invention, the chlorofluoromethane solution includes at least an organic solvent medium (e.g., acetone, dimethylformamide).

10 An alternative aspect of the present invention relates to pharmaceutical compositions produced by the various processes described herein.

## **BRIEF DESCRIPTION OF THE DRAWINGS**

Further features and advantages will become apparent from the following and more  
15 particular description of the preferred embodiments of the invention, as illustrated in the accompanying drawings, and in which like referenced characters generally refer to the same parts or elements throughout the views, and in which:

FIGURE 1 is a schematic illustration of a prior art process route for a fluticasone derivative, namely, fluticasone propionate;

20 FIGURE 2 is a schematic illustration of one embodiment of the synthesis step for 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester according to the invention;

FIGURES 3 and 4 are graphs showing reaction progression during synthesis of  
25 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester with NaI according to the invention;

FIGURE 5 is a graph showing reaction progression during synthesis of fluticasone propionate with NaI according to the invention; and

FIGURE 6 is a graph showing a comparison of reaction progression during  
synthesis of fluticasone propionate with and without NaI according to the invention.

## **DETAILED DESCRIPTION OF THE INVENTION**

Before describing the present invention in detail, it is to be understood that this invention is not limited to particularly exemplified compositions or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is  
5 for the purpose of describing particular embodiments of the invention only, and is not intended to limit the scope of the invention in any manner.

All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entirety.

It must be noted that, as used in this specification and the appended claims, the  
10 singular forms "a," "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a reagent" includes a mixture of two or more such reagents, reference to "an organic solvent" includes mixtures of two or more such solvents, and the like.

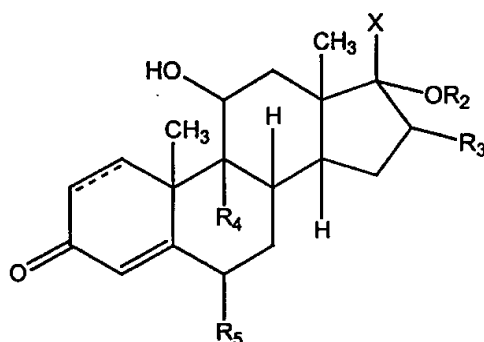
### **Definitions**

15 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although a number of methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

20 In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

By the term "fluticasone derivatives", as used herein, it is meant to mean and include compounds having at least the following core formulation:

(1)



wherein

X is an organic or inorganic moiety;

5  $R^2$  represents a  $-(C=O)$  lower (i.e.,  $C_{1-6}$ ) alkyl,  $-(C=O)$  aryl or  $-(C=O)$  heteroaryl;

$R^3$  represents a hydrogen atom or a lower alkyl (a methyl group which may be in either the  $\alpha$ - or  $\beta$ - configuration) or a methylene group or an oxygen atom bonded to a carbon atom;

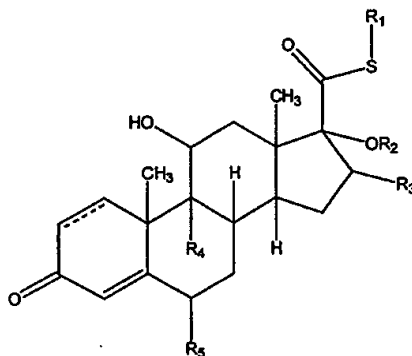
$R^4$  and  $R^5$  represent a fluorine atom; and

the symbol  $\text{-----}$  represents a single or double bond.

10

The term "fluticasone derivatives" thus includes, but is not limited to, compounds of the following formula:

(2)



15

wherein

$R_1$  represents a fluoromethyl, chloromethyl or bromomethyl group or a 2'- fluoroethyl group;  $R_2$  represents  $-(C=O)$ -aryl or  $-(C=O)$ -heteroaryl;  $R_3$  represents hydrogen, methyl

20 (which may be in either the  $\alpha$  or  $\beta$  configuration) or methylene group;  $R_4$  and  $R_5$  are the same or different and each represents hydrogen or halogen, such as fluorine; and the symbol  $\text{-----}$  represents a single or double bond.

The term "fluticasone derivatives" thus specifically includes 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrost-1,4-diene-17 $\beta$ -

carbothioic acid S-fluoromethyl ester.

By the term "mild base medium", as used herein, it is meant to mean a substance (i.e., a base) having a pH in the range of 8 to 12, more preferably, in the range of 8.5 to 10, including, but not limited to, inorganic bases, such as potassium hydrogen carbonate and sodium hydrogen carbonate, and organic bases, such as pyridine and collidine.

By the term "organic solvent medium", as used herein, it is meant to mean a substance capable of dispersing one or more other substances, including, but not limited to, a lower alkyl ketone (e.g., acetone, methyl ethyl ketone and methyl isobutyl ketone), a lower alkylamide (e.g., dimethylformamide and dimethylacetamide), esters (e.g., ethyl acetate and isopropyl acetate), and other like solvents.

By the term "iodide medium", as used herein, it is meant to mean a compound having at least one iodine atom, including, but not limited to, sodium iodide, potassium iodide, tetraalkyl ammonium iodide (e.g., tetramethyl ammonium iodide), and other like compounds.

By the term "pharmaceutical" or "pharmaceutical composition", as used herein, is meant to mean and include any compound or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. The term therefore encompasses those compounds or chemicals traditionally regarded as actives or drugs, as well as biopharmaceuticals including molecules such as peptides, hormones, nucleic acids, gene constructs and the like.

The "pharmaceuticals" or "pharmaceutical compositions", alone or in combination with other actives (or agents), typically include one or more added materials such as carriers, vehicles, and/or excipients. "Carriers," "vehicles" and "excipients" generally refer to substantially inert materials that are nontoxic and do not interact with other components of the composition in a deleterious manner. These materials can be used to increase the amount of solids in particulate pharmaceutical compositions. Examples of suitable carriers include water, fluorocarbons, silicone, gelatin, waxes, and like materials. Examples of normally employed "excipients," include pharmaceutical grades of carbohydrates including monosaccharides, disaccharides, cyclodextrins, and polysaccharides (e.g., dextrose, sucrose, lactose, raffinose, mannitol, sorbitol, inositol, dextrins, and maltodextrins); starch; cellulose; salts (e.g., sodium or calcium phosphates,

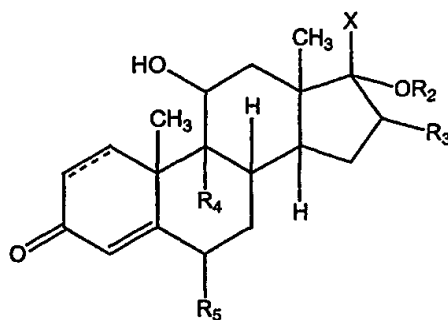


calcium sulfate, magnesium sulfate); citric acid; tartaric acid; glycine; low, medium or high molecular weight polyethylene glycols (PEG's); pluronics; surfactants; and combinations thereof.

As will be appreciated by one having ordinary skill in the art, the method of preparing fluticasone derivatives in accordance with the present invention substantially reduces or eliminates the disadvantages and drawbacks associated with conventional means of preparing fluticasone derivatives. A key advantage of the invention is the elimination of bromofluoromethane, a highly toxic, ozone-depleting substance, as a process reagent.

As indicated above, the term "fluticasone derivatives" includes compounds having at least the following core formulation:

(1)



wherein

X is an organic or inorganic moiety;

R<sup>2</sup> represents a – (C=O) lower alkyl, – (C=O) aryl or – (C=O) heteroaryl;

R<sup>3</sup> represents a hydrogen atom or a lower (i.e., C<sub>1-6</sub>) alkyl (a methyl group which may be in either the α- or β- configuration) or a methylene group;

R<sup>4</sup> and R<sup>5</sup> represent a fluorine atom; and

the symbol  $\text{-----}$  represents a single or double bond.

Illustrative "fluticasone derivatives" are described in detail in Phillipps, et al. and Israel No. 109,656 (discussed above); U.S. Pat. Nos. 4,335,121, 4,093,721, 3,828,080,

3,989,686 and 3,067,197; GB Pat. Nos. 1384372, 1438940 and 1517278; and Germany Pat. Nos. 2538596 and 2336693, which are incorporated by reference herein.

Referring now to Fig. 1, there is shown a conventional process route for a well known fluticasone derivative, namely, fluticasone propionate. The fluticasone propionate process route shown in Fig. 1 is discussed in detail in Phillipps, et al., which is  
5 incorporated by reference herein.

As illustrated in Fig. 1, the synthesis step in the noted process involves the use of bromofluoromethane (BFM) as a reactant with thioacid propionate. As indicated above, although BFM is highly toxic, BFM is typically employed as a reactant during the  
10 preparation of most, if not all, fluticasone derivatives.

Referring now to Fig. 2, there is shown the synthesis step for 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrost-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester in accordance with one embodiment of the invention. As illustrated in Fig. 2, in contrast to the conventional process illustrated in  
15 Fig. 1, chlorofluoromethane ("CFM") is employed as a reagent to effectuate synthesis of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrost-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester. The need to employ bromofluoromethane as a reagent to effectuate synthesis of the noted fluticasone derivative is thus eliminated.

Fig. 2 further reflects that in one embodiment, CFM is in solution with at least an "iodide medium" (e.g., sodium iodide) and a "mild base medium" (e.g., potassium hydrogen carbonate) to effectuate synthesis of the fluticasone derivative. Thus, in accordance with one embodiment of the invention, at least an iodide and mild base medium are in solution with CFM. Preferably, the iodide medium comprises sodium  
20 iodide and the mild base medium comprises potassium hydrogen carbonate.

As will be appreciated by one having ordinary skill in the art, the CFM solution can also contain an "organic solvent medium" (e.g., acetone, DMF) with or without H<sub>2</sub>O to facilitate the synthesis of the fluticasone derivatives.

In an additional envisioned embodiment of the invention, the CFM is in solution with at least one of the aforementioned mild base mediums. In this embodiment, the use of  
30 the "iodide medium" is thus eliminated.

As will be appreciated by one having ordinary skill in the art, the elimination of the

iodide medium and, in particular, sodium iodide eliminates the possibility of the formation of iodofluoromethane, a potential synthetic intermediate product. Applicants have also found that the elimination of the iodide medium enhances the synthesis of fluticasone derivatives (i.e., faster rate) and potentially reduces undesirable by-products.

5 Applicants have further found that rapid introduction of CFM to the solution during the synthesis step further reduces the possibility of forming undesirable by-products. Thus, in a preferred embodiment of the invention, a substantial portion, more preferably, all the CFM is completely introduced to the solution during the synthesis step in a period no greater than 5 min.

10 As indicated above, it has also been found that CFM remains in solution during the synthesis of fluticasone derivatives and, hence, is reactive above its boiling point of  $-9.1^{\circ}\text{C}$ . The noted reaction (i.e., chemical synthesis) can thus be effectuated at elevated temperatures.

It is well known that increasing the reaction temperature will generally drive  
15 chemical synthesis at a greater rate. The physical limit on the temperature imposed is typically the flash point (or boiling point) of the reagent (e.g., CFM) from the solvent.

Thus, in accordance with the invention, the CFM reaction temperature is maintained in the range of approximately  $-60^{\circ}\text{C}$  to  $90^{\circ}\text{C}$ , preferably,  $-20^{\circ}\text{C}$  to  $60^{\circ}\text{C}$ , more preferably,  $-15^{\circ}\text{C}$  to  $50^{\circ}\text{C}$ . Even more preferably, the CFM reaction temperature is  
20 in the range of approximately  $-15^{\circ}\text{C}$  to  $25^{\circ}\text{C}$ .

It is further well known that increasing the reagent concentration will similarly increase the rate of chemical synthesis. However, in the present invention, it has been found that increasing the CFM concentration above 1 molar equivalent to the thioacid furoate does not yield a significant increase in the production of viable product (i.e.,  
25  $6\alpha,9\alpha$ -difluoro- $17\alpha$ -[(2-furanylcarbonyl)oxy]- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxoandrosta-1,4-diene- $17\beta$ -carbothioic acid S-fluoromethyl ester). A similar observation has been made during the preparation of other fluticasone derivatives and, in particular, fluticasone propionate.

Accordingly, since a single equivalent of CFM may be employed, the following  
30 advantages can be realized: (1) reduction in the risk of environmental release of CFM during processing and (2) substantial reduction or elimination of excess CFM in the reaction mix.

As will be appreciated by one having ordinary skill in the art, although the synthesis steps for 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester shown in Fig. 2 reflect CFM reaction with thioacid furoate, the CFM synthesis reaction shown in the noted figure and discussed in detail above is readily effectuated with all thiocarboxylic acids.

The following examples illustrate the process of the invention. The examples are for illustrative purposes only and are not meant to limit the scope of the invention in any way.

The following abbreviations, symbols and acronyms are employed in the examples. Unless defined otherwise, all abbreviations, symbols, acronyms, technical and scientific terms employed herein have the same meaning as commonly understood by one having ordinary skill in the art.

"NaI"---sodium iodide

"KHCO<sub>3</sub>"---potassium hydrogen carbonate

"DMF"---dimethylformamide

"TA"---"thioacid" (i.e., (6 $\alpha$ , 11 $\beta$ , 16 $\alpha$ , 17 $\alpha$ )-6,9-Difluoro-11,17-dihydroxy-16-methyl-3 oxoandrosta-1,4-diene-17-carbothioic acid)

"TF"---"thioacid furoate" (i.e., 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl- 3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid)

"FD"--- 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester

"TP"---"thioacid propionate" (i.e., 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$  -(propionyloxy)androsta-1,4-diene-17 $\beta$ -carbothioic acid)

"FP"---"fluticasone propionate" (alternative chemical names i.e., S-(Fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ , 17 dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta- 1,4-diene-17 $\beta$ -carbothioate, 17-propionate; a.k.a. S-fluoromethyl 6 $\alpha$ ,9 $\alpha$  -difluoro-11 $\beta$ - hydroxy-16 $\alpha$ -methyl-3-oxo- 17 $\alpha$ -propionyloxy)androsta- 1,4-diene-17 $\beta$ -carbothioate.)

"R1, B1"---reaction 1, batch 1; "R1, B2"---reaction 1, batch 2, etc.

"B1"---batch 1; "B2"---batch 2, etc

"RT"---room temperature

## EXAMPLE 1

**PREPARATION OF 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -(2-furanylcarbonyloxy)-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester**

5 Thioacid furoate ("TF") was initially prepared from a corresponding thioacid and converted to thioacid furoate. The purity of the thioacid furoate, which was determined by HPLC, was 91.8% with the major impurity being thioacid ("TA").

Chlorofluoromethane ("CFM") was obtained from SynQuest Laboratories Inc. in Alachua, Florida. As previously noted, according to the Montreal Protocol,  
 10 chlorofluoromethane is classified as an Annex C, Group 1 controlled substance. Its ozone-depleting capability value is 0.02 where bromofluoromethane is ranked as 0.73 and trichlorofluoromethane, CFC-11, is 1.0.

The remaining reagents were all ACS grade. The equivalents for all reactions are shown in Table I.

15

Table I

Reagent	R1, B1	R1, B2	R2, B1	R2, B2
TF	4 gm	4 gm	4 gm	4 gm
DMF	8 eq.	8 eq.	8 eq.	8 eq.
KHCO <sub>3</sub>	0.202 wt.	0.202 wt.	0.202 wt.	0.202 wt.
CFM	3 eq.	2 eq.	2 eq.	1 eq.
NaI	1 eq.	1 eq.	1 eq.	1 eq.

20 The reaction conditions for each batch are shown in Table II. All reactions were performed on the HEL autoMATE automated reaction platform.

Table II

Step	R1, B1	R1, B2	R2, B1	R2, B2
1	add TF	add TF	add TF	add TF
2	add DMF	add DMF	add DMF	add DMF
3	stir and cool to -15° C	stir and cool to -15° C	stir and cool to -15° C	stir and cool to -15° C
4	add KHCO <sub>3</sub> & NaI	add KHCO <sub>3</sub> & NaI	add KHCO <sub>3</sub> & NaI	add KHCO <sub>3</sub> & NaI
5	add CFM	add CFM	add CFM	add CFM
6	hold at -15° C for 20 hours	hold at -15° C for 29 hours	hold at -15° C for 15 minutes	hold at -15° C for 15 minutes

7	warm to RT ( $\geq 15$ min)	warm to RT ( $\geq 15$ min)	warm to 5° C ( $\geq 15$ min)	warm to 15° C ( $\geq 15$ min)
8	sample by HPLC to determine end- point	sample by HPLC to determine end- point	sample by HPLC to determine end- point	sample by HPLC to determine end- point

\*CFM was added by allowing the liquid to expand in a gas tight syringe and flow into the cooled reaction mixture.

Table III

Sample	R1, B1	R2, B1
1 hour	90.60% TF 2.06% TA 1.19% FD	91.28% TF 2.10% TA 0.82% FD
4 hours	75.48% TF 2.22% TA 9.78% FD	82.60% TF 2.07% TA 9.34% FD
20.5 hours	60.13% TF 1.74% TA 31.44% FD	59.45% TF 1.72% TA 33.60% FD
22.75 hours	57.13% TF 1.67% TA 34.10% FD	50.85% TF 1.70% TA 41.88% FD
23.75 hours	54.95% TF 1.67% TA 36.29% FD	27.61% TF 1.74% TA 64.84% FD
25.75 hours	48.12% TF 1.63% TA 43.11% FD	8.95% TF 1.65% TA 82.83% FD

5

Table IV

Sample	R1, B2	R2, B2
Start	90.17% TF 2.34% TA 0.85% FD	89.43% TF 2.41% TA 0.86% FD
2.5 hours	66.91% TF 2.26% TA 23.48% FD	63.62% TF 2.26% TA 16.51% FD
4 hours	57.26% TF 1.88% TA 35.19% FD	64.26% TF 2.02% TA 28.54% FD
6 hours	44.87% TF 1.91% TA 42.04% FD	46.88% TF 2.11% TA 36.61% FD

22 hours	15.22% TF 1.93% TA 76.56% FD	15.59% TF 1.89% TA 77.22% FD
24 hours	14.73% TF 1.99% TA 76.58% FD	9.53% TF 1.25% TA 85.31% FD

Table V

Reaction	R1, B1	R1, B2	R2, B1	R2, B2
Yield of FD	3.62 gm	3.31 gm	3.54 gm	3.51 gm
Percent	85.2%	77.9%	83.3%	82.6%
Purity profile*	4.90% TA 1.12% NaI 93.98% FD	0.09% TA 0.48% NaI 99.43% FD	0.09% TA 0.49% NaI 99.42% FD	0.00% TA 1.51% NaI 98.49% FD

\*Non-washed, filtered solids after stirring in water

The reaction products were dropped into a cold water/acid solution, i.e., 5° C, over approximately 10 minutes and stirred for at least an hour. Each product was then filtered in a fine glass filter funnel, dried by vacuum and then oven dried for at least 12 hours (see Tables III and IV above). The product(s) were then weighed to determine yield and assayed for purity (see Table V).

The above noted experimental data clearly indicates that the synthetic route for 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester using chlorofluoromethane instead of bromofluoromethane is viable. The elimination of the bromofluoromethane as a reagent has the advantage of making the process more environmentally friendly and potentially less expensive. It was further observed that after a known period of time, the reactors were all allowed to warm to room temperature, approximately 20° C.

As reflected in Table V, the purity of the yielded FD product was greater than 93% for all samples. As will be appreciated by one having ordinary skill in the art, higher purity levels of FD product can be obtained by performing the synthesis at a higher temperature wherein the starting thioacid furoate is entirely consumed. Indeed, reactions performed at lower temperatures are more prone to allow side reactions to proceed and, hence, can produce an unacceptable impurity profile.

The residual sodium iodide in the final product, as exhibited in all reactions, further indicates that additional washing of the final product is likely to increase the purity to greater than 99.5%.

Further, the reaction continued on despite the fact that this is well above the  
5    -9.1° C boiling point of CFM. This led to the additional study of the solubility of CFM in dimethylformamide ("DMF"). DMF was cooled in a dry ice/acetone bath and CFM was dosed in. Samples were taken for FTIR analysis and the result was that the CFM was present at room temperature. The solution was then heated and the CFM was driven out at  
23° C. The results indicated that the process limit for the upper temperature is around 20°  
10   C where the CFM stays soluble in the DMF and, at this temperature, there is a subsequent increase in the reaction rate (see Example 2).

Referring now to Figs. 3 and 4, there is shown the reaction progression for 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester as determined by HPLC. It should be noted that  
15   the percentages (i.e., Y axis) are solution values in Figs 3-6. The isolated material percentages are higher.

What is clearly evident is that in the first batch of reactions (referred to as B1 in Fig. 3) the reaction proceeds very slowly until the reaction is warmed to room temperature. It is apparent that the reaction will not only proceed faster at an elevated  
20   temperature, but the CFM remains available to react.

In the second batch of reactions (referred to as R2 in Fig. 4), the only differences were that reaction 1- batch 2 (R1, B2) was at 5° C and had 1 equivalent of CFM while reaction 2 was held at 15° C and had 2 equivalents of CFM added. As illustrated in Figs. 3 and 4, it can be seen that the reaction curves are almost identical and actually converge at  
25   approximately 22 hours.

Figures 3 and 4 are plots of the percentages of analytes of interest as determined by the Area Normalization Methods described in the British Pharmacopoeia for the display of HPLC data as a function of time. The "Percent" of the Y-axis is the Percent Area. The method takes the total area of all peaks of interest and displays the percentage of the total  
30   that is due to a particular analyte. Figures 5 and 6 are similar plots but show only the result for the final product.



**EXAMPLE 2****Preparation of Fluticasone Propionate with Sodium Iodide**

Thioacid propionate ("TP") was initially prepared from a corresponding thioacid and converted to thioacid propionate using the process route shown in Fig. 1. The purity of the thioacid propionate, which was determined by HPLC, was 90.5%. The major impurities were thioacid (2.12%) and diethylamine (2.10%).

Chlorofluoromethane ("CFM") was similarly obtained from SynQuest Laboratories Inc. in Alachua, Florida. The remaining reagents were all ACS grade.

The equivalents for all reactions are shown in Table VI.

Table VI

Reagent	R1	R2
TP	6.85 grams	6.32 grams
DMF	4.5 eq.	4.9 eq.
KHCO <sub>3</sub>	0.245 wt.	0.266 wt.
CFM	1.5 eq.	1 eq.
NaI	1 eq.	1 eq.

The reaction conditions for each batch are shown in Table VII. All reactions were similarly performed on the HEL autoMATE automated reaction platform.

Table VII

Step	R1	R2
1	add TP	add TP
2	add DMF	add DMF
3	stir and cool to -10° C	stir and cool to -5° C
4	add KHCO <sub>3</sub> and NaI	add KHCO <sub>3</sub> and NaI
5	add CFM*	add CFM*
6	hold at -10° C for 5 hrs.	Hold at -5° C for 15 min.
7	warm to RT (≥15 min)	warm to 20° C (≥15 min)
8	sample by HPLC to determine end-point.	sample by HPLC to determine end-point.

\*CFM was added by allowing the liquid to expand in a gas tight syringe and flow into the cooled reaction mixture.

The reaction products were similarly dropped into a cold water/acid solution, i.e., 5° C, over approximately 10 minutes and stirred for at least an hour. The products were then filtered in a fine glass filter funnel, dried by vacuum, and then oven dried for at least 12 hours at 30° C under vacuum. The products were then weighed to determine yield and assayed for purity (see Table VIII).

Table VIII

Reaction	R1	R2
Yield FP (mwt corrected)	7.08 grams	5.99 grams
Percent	96.7%	88.7%
Purity profile*	0.14% TA 0.17% NaI 0.04% KHCO <sub>3</sub> 99.65% FP	0.00% TA 0.00% NaI 3.99% KHCO <sub>3</sub> 96.01% FP

\*Non-washed, filtered solids after stirring in water

Referring to Fig. 5, it can be seen that the first reaction (R1) proceeded very slowly until the reaction was warmed to room temperature. In the second reaction (R2), the only difference was that the batch was warmed to 20° C once the CFM was added. As illustrated in Fig. 5, the warmed reaction proceeded considerably faster, while both reactions (R1, R2) converged at approximately 90% in 20 hours.

This example further demonstrates that there are viable alternative synthetic routes for preparing fluticasone derivatives, and, in particular, fluticasone propionate, without the necessity of employing bromofluoromethane as a reagent.

### EXAMPLE 3

#### Preparation of Fluticasone Propionate without Sodium Iodide (NaI)

Thioacid propionate was initially prepared from a corresponding thioacid and converted to thioacid propionate. Similar side-by-side reactions, as shown in Example 2, were then conducted. The equivalents for each reaction are shown in Table IX.

Each reaction was followed by HPLC, and final products were verified by HPLC and IR Spectroscopy.

Table IX

Reagent	R1	R2
TP	4 gm	4 gm
DMF	8 eq.	8 eq.
KHCO <sub>3</sub>	0.202 wt.	0.202 wt.
CFM	1.5 eq.	1.5 eq.
NaI	1 eq.	none

5 HPLC analysis reflected that the reaction without NaI (R2) proceeded considerably faster than the reaction with NaI (see Fig. 6). Referring now to Table X, the reaction without NaI also yielded a higher percentage of "high purity" product (i.e., FP). As will be appreciated by one having ordinary skill in the art, the noted observations are also applicable to the synthesis of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-  
 10 16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester.

Table X

Reaction	R1 (w/NaI)	R2 (w/o NaI)
Yield FP (mwt corrected)	5.46 gm	5.64 gm
Percent	85%	88%
Purity profile*	0.88% TA 0.21% TP 0.58% NaI 99.21% FP	0.49% TA 0.11% TP 0.0% NaI 99.4% FP

\*Non-washed, filtered solids after stirring in water

15 This example thus demonstrates that high purity fluticasone propionate can be prepared with or without BFM and NaI. As stated above, it will be appreciated by one having ordinary skill in the art that high purity 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester similarly can be prepared with or without BFM and NaI. Synthesis of  
 20 the noted fluticasone derivatives is also achieved at a faster rate and produces a higher yield of final products. Further, by eliminating NaI the probability of forming by-products

is substantially reduced, and the possibility of forming iodide-containing by-products is eliminated.

Without departing from the spirit and scope of this invention, one of ordinary skill can make various changes and modifications to the invention to adapt it to various usages and conditions. As such, these changes and modifications are properly, equitably, and intended to be, within the full range of equivalence of the following claims.

5

**CLAIMS**

What is Claimed is:

1. A process for preparing 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester  
5 comprising reacting 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid with a solution containing chlorofluoromethane and a mild base medium at a reaction temperature in the range of approximately -20° C to 60° C.
2. The process of Claim 1, wherein said reaction temperature is in the range of  
10 approximately -15° C to 25° C.
3. The process of Claim 1 or claim 2, wherein said mild base medium has a pH less than approximately 12.
4. The process of Claim 1, 2 or 3, wherein said mild base medium has a pH in the range of approximately 8.5 to 10.
- 15 5. The process of any one of Claims 1 to 4, wherein said mild base medium comprises an inorganic base selected from the group consisting of potassium hydrogen carbonate and sodium hydrogen carbonate.
6. The process of any one of Claims 1 to 4, wherein said mild base medium comprises an organic base selected from the group consisting of pyridine and collidine.
- 20 7. The process of any one of Claims 1 to 6, wherein said solution includes an organic solvent medium.
8. The process of Claim 7, wherein said organic solvent medium comprises a lower alkyl ketone selected from the group consisting of acetone, methyl ethyl ketone and methyl isobutyl ketone.
- 25 9. The process of Claim 7, wherein said organic solvent medium comprises a lower alkylamide selected from the group consisting of dimethylformamide and dimethylacetamide.
10. The process of Claim 7, wherein said organic solvent medium comprises an ester selected from the group consisting of ethyl acetate and isopropyl acetate.
- 30 11. The process of any one of Claims 1 to 10, wherein said chlorofluoromethane is introduced into said solution over a period no greater than 5 min.

12. The process of any one of Claim 1 to 11, wherein said solution includes water.

13. The process of any one of Claims 1 to 12, wherein said solution includes an iodide medium selected from the group consisting of sodium iodide, potassium iodide and tetraalkyl ammonium iodide.

14. A pharmaceutical composition having at least a first medicament obtained by reacting 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrost-1,4,-diene-17 $\beta$ -carbothioic acid with a solution containing chlorofluoromethane and a mild base medium at a reaction temperature in the range of approximately -20° C to 60° C.

15. The pharmaceutical composition of Claim 14, wherein said reaction temperature is in the range of approximately -15° C to 25° C.

16. The pharmaceutical composition of Claim 14, wherein said first medicament comprises 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrost-1,4,-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester.

17. The pharmaceutical composition of any one of Claims 14 to 16, wherein said mild base medium has a pH less than approximately 12.

18. The pharmaceutical composition of Claim 17, wherein said mild base medium has a pH in the range of approximately 8.5 to 10.

19. The pharmaceutical composition of any one of Claim 14 to 18, wherein said mild base medium comprises an inorganic base selected from the group consisting of potassium hydrogen carbonate and sodium hydrogen carbonate.

20. The pharmaceutical composition of any one of Claims 14 to 18, wherein said mild base medium comprises an organic base selected from the group consisting of pyridine and collidine.

21. The pharmaceutical composition of any one of Claims 14 to 20, wherein said solution includes an organic solvent medium.

22. The pharmaceutical composition of Claim 21, wherein said organic solvent medium comprises a lower alkyl ketone selected from the group consisting of acetone, methyl ethyl ketone and methyl isobutyl ketone.

23. The pharmaceutical composition of Claim 21, wherein said organic solvent medium comprises a lower alkylamide selected from the group consisting of

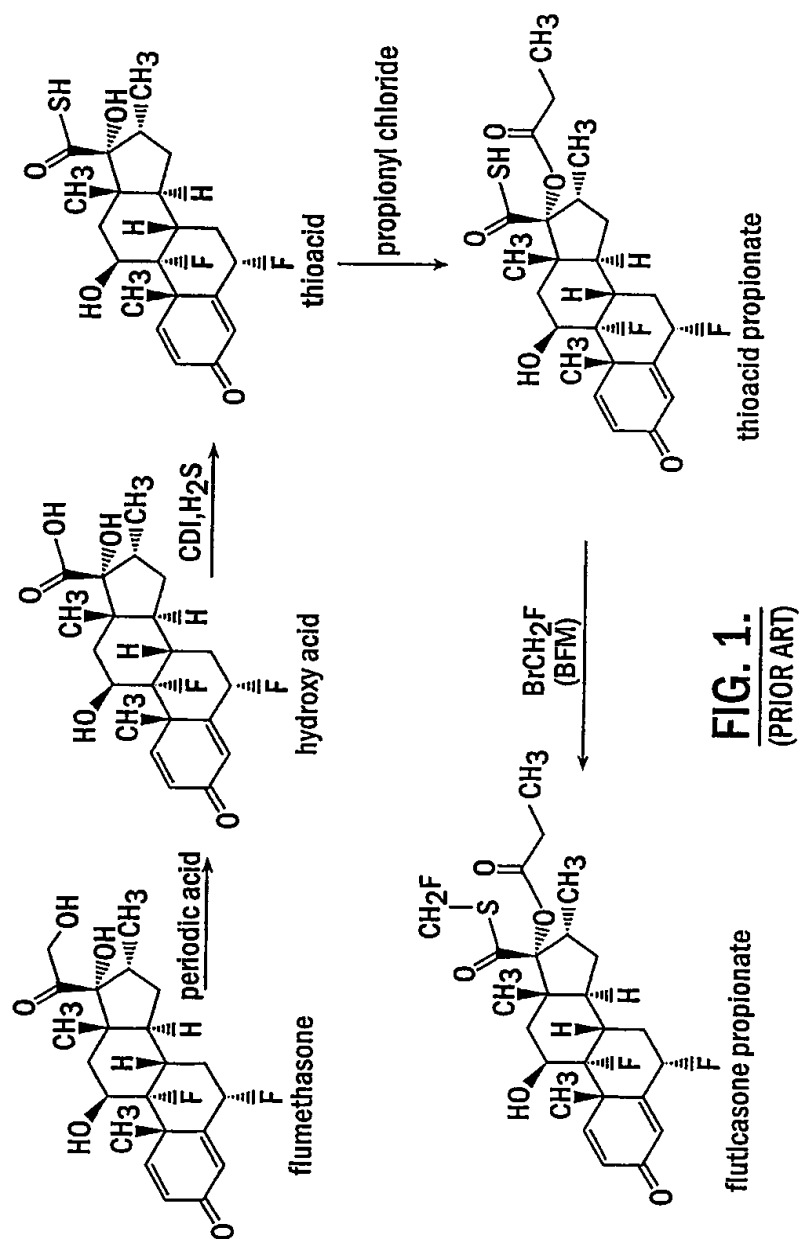
dimethylformamide and dimethylacetamide.

24. The pharmaceutical composition of Claim 21, wherein said organic solvent medium comprises an ester selected from the group consisting of ethyl acetate and isopropyl acetate.

5           25. The pharmaceutical composition of any one of Claims 14 to 24, wherein said chlorofluoromethane is introduced into said solution over a period no greater than 5 min.

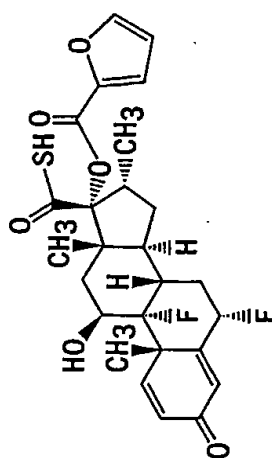
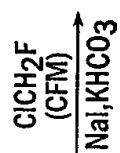
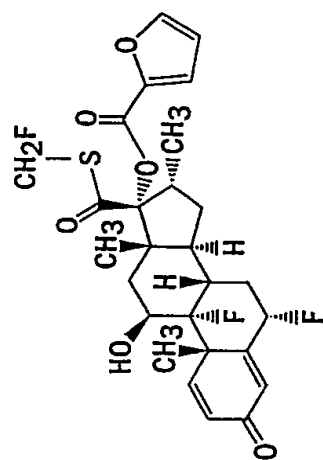
26. The pharmaceutical composition of any one of Claims 14 to 25, wherein said solution includes water.

10           27. The pharmaceutical composition of any one of Claims 14 to 26, wherein said solution includes an iodide medium selected from the group consisting of sodium iodide, potassium iodide and tetraalkyl ammonium iodide.





2/4

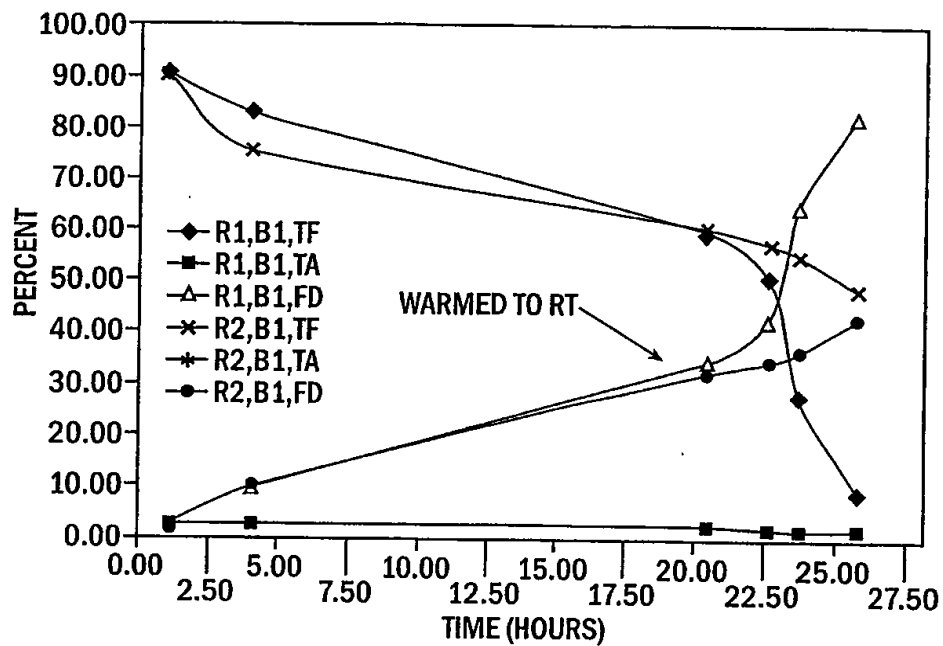
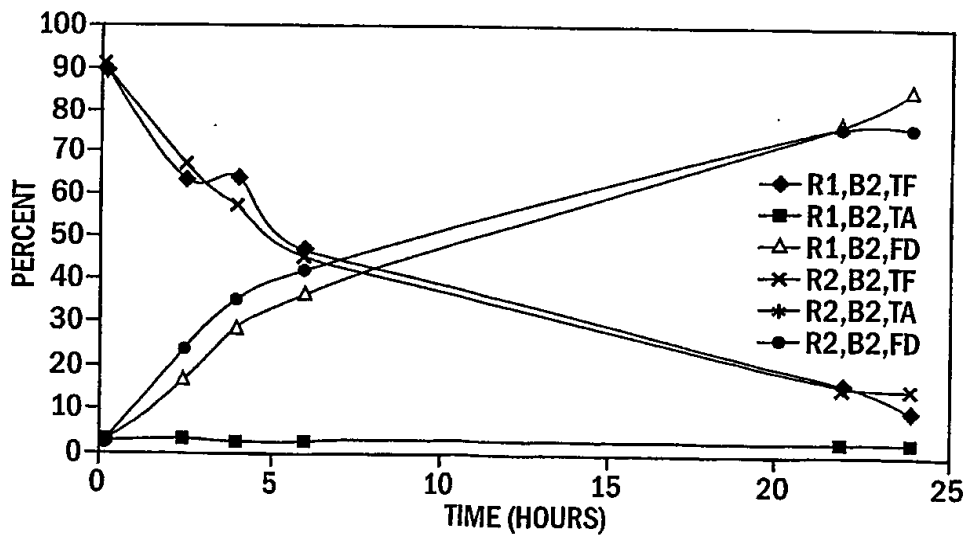


Thioacid Furoate

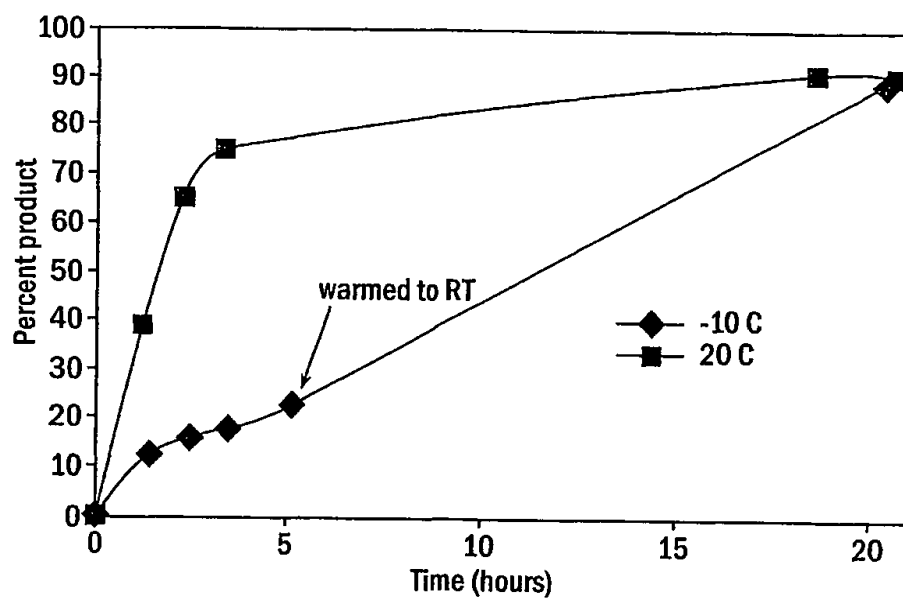
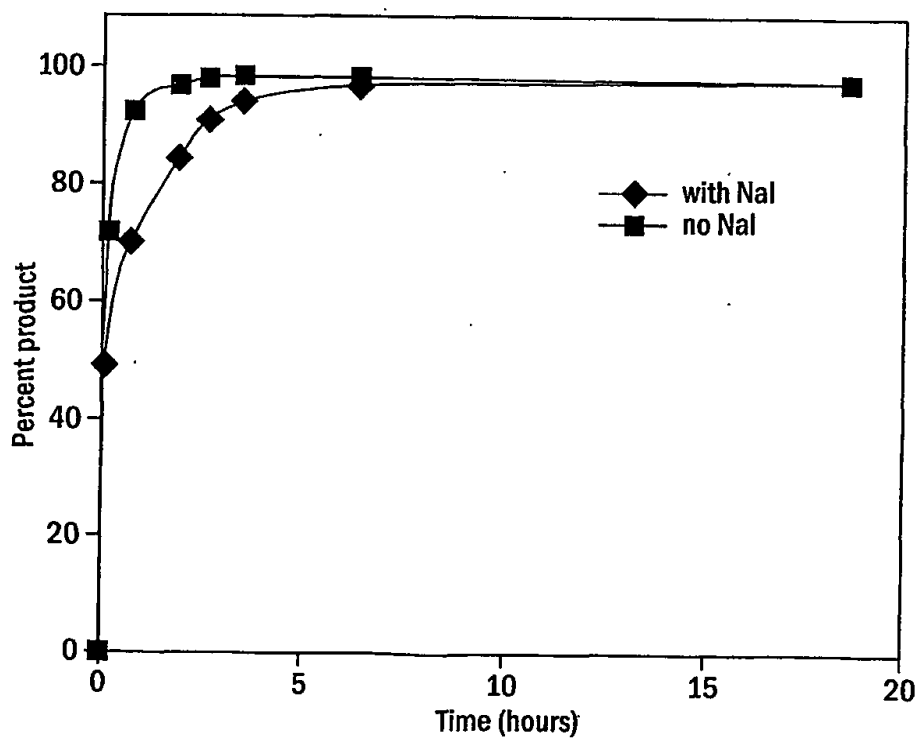
6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid      6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester

**FIG. 2.**

3/4

FIG. 3.FIG. 4.

4/4

**FIG. 5.****FIG. 6.**